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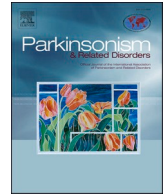
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Review article

Digital health technology for non-motor symptoms in people with Parkinson's disease: Futile or future?

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ABSTRACT

Introduction: There is an ongoing digital revolution in the field of Parkinson's disease (PD) for the objective measurement of motor aspects, to be used in clinical trials and possibly support therapeutic choices. The focus of remote technologies is now also slowly shifting towards the broad but more "hidden" spectrum of non-motor symptoms (NMS).

Methods: A narrative review of digital health technologies for measuring NMS in people with PD was conducted. These digital technologies were defined as assessment tools for NMS offered remotely in the form of a wearable, downloadable as a mobile app, or any other objective measurement of NMS in PD that did not require a hospital visit and could be performed remotely. Searches were performed using peer-reviewed literature indexed databases (MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials), as well as Google and Google Scholar.

Results: Eighteen studies deploying digital health technology in PD were identified, for example for the measurement of sleep disorders, cognitive dysfunction and orthostatic hypotension. In addition, we describe promising developments in other conditions that could be translated for use in PD.

Conclusion: Unlike motor symptoms, non-motor features of PD are difficult to measure directly using remote digital technologies. Nonetheless, it is currently possible to reliably measure several NMS and further digital technology developments are underway to offer further capture of often under-reported and under-recognised NMS.

1. Introduction

The use of digital health technology, some in combination with connected devices (e.g. smartphones), is on the rise to improve the management of medical conditions, including Parkinson's disease (PD).

Digital health technology covers a broad area of technical applications and includes devices worn on the body (in the form of watches, bracelets or devices embedded in clothing), smartphones, sensors embedded into a patient's home (for example in smart beds) or analysis of regularly used appliances, such as computer keyboards. Ideally, such remote

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measurement techniques should be non-disruptive to the person's normal lifestyle. Specifically, the technology should allow for use anywhere without barriers, and should be feasible for use both at home and within the community. Digital technologies theoretically provide an opportunity to monitor people for extended periods of time, provided that participants comply with extended use, which has been a vexing issue in most studies thus far. Additionally, digital technologies potentially allow for care to be delivered at home and in the community, thereby limiting the need for hospital visits [1]. Importantly, these technologies enable us to passively collect data in the background, and these data are therefore not influenced by rater or patient bias, which is often the case with subjective patient diaries [2]. Another concern with existing approaches is the attentional compensation which is typically associated with in-clinic sessions while patients know they are being observed [3]. In fact, these benefits have already led to the invention and testing for usefulness and reliability for many devices in PD and neurocognitive disorders [4], some of which have already made their way into clinical practice [5]. However, in the case of PD, the focus of digital technology has been almost exclusively on the motor symptoms associated with this disease, with devices measuring tremor, bradykinesia, wearing-off, dyskinesia, gait patterns and falls [6,7]. Attempts have even been made to measure rigidity objectively [8]. Non-motor symptoms (NMS), which are pivotal to the natural history of PD and which are a crucial determinant of the patient's and caregiver's quality of life, have thus far received little attention as a target for objective measurements through digital technology, although the introduction of commercial systems to record heart rate, ECG and blood oxygen saturation has raised the interest from both patients and healthy subjects.

Monitoring and measurement of NMS in PD is complicated by the physiology of certain NMS which makes it difficult to objectively measure them, not only from a digital health perspective. Similarly, dedicated non-motor scales are not always able to detect and correctly identify NMS [9], also bearing in mind these scales measure patient or clinician reported outcomes and not physiological processes. To date, the only relatively well-explored NMS aspect of PD in which wearable technology has been deployed, is the use of actigraphy for circadian and sleep disorders [10]. However, in recent years attempts have been made to address the objective assessment of some other NMS in PD. In addition to the dual challenge posed by first objectively measuring NMS and then transforming this into digital health outcomes, there is the lack of clear guidelines and criteria for the selection, technical validation, and clinical validation of novel digital endpoints [11]. The use of technology-based digital devices should aim to supplement objective measures as well as the more commonly used subjective measures, including scales and questionnaires, in determining presence and severity of symptoms in the clinical management of PD beyond research projects [12,13]. In this narrative review we aim to describe the state of the art of digital health technology for objective assessment of NMS in PD.

2. Methods

We performed a review of digital health technology relating to NMS occurring in PD. The objectives of this review were to summarise the different types of digital technology currently in use to measure NMS in PD, as well as those technologies that hold promise for future use in PD, and to inform future non-motor research and health policies. The aim of this review was to provide a narrative overview and viewpoint of digital health technologies for NMS in PD, rather than a systematic review.

The search strategy included the terms 'Parkinson' or 'Parkinson's' combined with 'gyroscope', 'accelerometer', 'technology', 'app' or 'wearable'. The search was not limited by date, language, or study design. The searches were performed using peer-reviewed literature indexed databases (MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials), as well as Google and Google Scholar by the first and second authors and

conflicts were resolved with the senior authors of the manuscript. Reference lists of identified manuscripts were used to identify any other relevant studies. The final search was performed in December 2020. For the purpose of this review, digital technology was defined as digital assessment tools for NMS offered remotely in the form of a wearable, downloadable as a mobile app, or any objective digital measurement of NMS in PD that did not require a hospital visit and could be performed at home. Inclusion criteria were: 1) studies addressing digital health technology in people with Parkinson's disease, and 2) measurement and/or monitoring of non-motor symptoms. Exclusion criteria were: 1) digital technologies in populations other than people with Parkinson's disease, and 2) measurement and/or monitoring of motor symptoms.

3. Results

An overview of the 18 studies with identified technologies measuring NMS and wearable outcomes associated with NMS is provided in Table 1 and examples are given in Fig. 1.

3.1. Overall non-motor symptoms

Currently, no objective measurements of general non-motor burden is available. Even though certain apps have used the availability of patients scoring self-reported outcome measures [14], these are still subjective and come with the limitations of patient completed diaries.

3.2. Orthostatic hypotension

Among Parkinson's-related cardiovascular abnormalities, orthostatic hypotension (OH) is the most common and one of the better described conditions with an overall prevalence ranging from 10% to 70%. OH is multifactorial in origin, as it can be iatrogenic, but also an intrinsic feature of PD occurring early in the course of the disease [15], as well as in the prodromal phase [16], with neuropathological studies confirming the presence of pathological alpha-synuclein deposits in central and peripheral regulatory nuclei [17]. In addition to OH, supine hypertension and nocturnal hypertension are other common problems in PD and detection is required as OH is associated e.g. with white matter lesions [18].

The gold standard for OH diagnosis is a standard blood pressure measurement in the supine and upright position or a head-up-tilt test in hospital settings, and for detection of supine or nocturnal hypertension the use of 24-h home monitoring [19]. Scaling down the standard devices used for this, would enable blood pressure measurement in a home environment. For example, Hellman et al. reported continuous non-invasive arterial pressure monitoring in PD in patients who had documented OH compared to those without OH [20]. They showed that the wearable device was capable of reproducing findings made in a hospital setting, which was considered the 'gold standard' in this study. Valleslonga et al. compared ambulatory blood pressure monitoring (ABPM) for OH with office blood pressure measurement [21] to test the diagnostic accuracy of ABPM-based hypotensive episodes (Hypo-ep) and hypotension during periods of wakefulness (Hypo-aw). They showed a diagnostic accuracy of 87.6% to detect OH, suggesting that remote monitoring of blood pressure is feasible although the large device and monitor size are limitations.

Further developments are likely to be expected to take on the form of smart watches. Several of such watches are in existence and are capable of measuring heart rate, blood pressure, and oxygen saturation. Currently, however, it would seem that only heart rate meets accuracy guidelines, but not the other vital sign measurements [22,23].

3.3. Sleep dysfunction

Sleep dysfunction, such as onset and maintenance insomnia, are a common feature occurring in PD although with wide range estimate

Table 1

Remote monitoring devices for non-motor symptoms in Parkinson's disease. Abbreviations: OH: orthostatic hypotension; PD: Parkinson's disease; RBD: Rapid Eye Movement Sleep Behavioural Disorder; PDSS: Parkinson's disease sleep scale; PSG: polysomnography; NMSQ: Non Motor Symptoms Questionnaire; MMSE: Mini Mental State Examination.

Non motor symptom	Study	Remote monitoring device	Number of participants and duration of monitoring	Validation against	Measure used and findings
Orthostatic hypotension and cardiovascular	Hellman et al., 2015 [20]	Scaled down wearable blood pressure monitor	•52 participants (31 with OH and 21 without) •One-off session of 3 min	In clinic blood pressure measurements	Continuous non-invasive arterial blood pressure. Similar proportion of participants with OH for both devices
	Vallelonga et al., 2019 [21]	Scaled down wearable blood pressure monitor	•113 participants •24 h blood pressure monitoring	In clinic blood pressure measurements	Continuous non-invasive arterial blood pressure. Two or more episodes with ≤ 15 mmHg systolic drop 75% diagnostic accuracy for OH. One or more episodes 93% specificity for OH
Sleep	Nass and Nass 2008 [74]	Actigraphy (triaxial wrist-worn device)	•17 participants with PD •69 healthy controls •3 days and nights	None	Activity measure between participants with PD and controls differ significantly, particularly at nighttime
	Perez-Lloret et al., 2009 [29]	Actigraphy (triaxial wrist-worn device)	•71 participants with PD •21 healthy controls •7 days and nights	PDSS	Significant moderate correlations between actigraphy and PDSS domains
	Stavitsky et al., 2010 [75]	Actigraphy (triaxial wrist-worn device)	•30 participants with PD •14 healthy controls •7 days and nights	Sleep diary PDSS	Scores on subjective sleep correlated moderately with actigraphy-derived estimates, but only in participants with PD
	Naismith et al., 2010 [30]	Actigraphy (triaxial wrist-worn device)	•22 participants with PD •2 weeks	Epworth Sleepiness Scale REM Sleep Behaviour Questionnaire Scales for Outcomes in Parkinson's disease (SCOPA) Sleep	Participants with RBD had higher number of activity bouts than those without RBD
	Maglione et al., 2013 [10]	Actigraphy (triaxial wrist-worn device)	•61 participants with PD •1 night	PSG	Significant moderate correlations between actigraphy and polysomnography measures for sleep time and wake after sleep onset
	Louter et al., 2014 [31]	Actigraphy (triaxial wrist-worn device)	•45 participants with PD •1 night	PSG	For predicting RBD 95 wake bouts per night on actigraphy had 95.5% specificity, 20.1% sensitivity 85.7% positive predictive value compared to PSG
	Gunn et al., 2014 [76]	Actigraphy (triaxial wrist-worn device)	•95 participants with PD •48 healthy controls •2 weeks	Digit Span Backwards subtest (raw score) of the Wechsler Adult Intelligence Scale-III (WAIS-III)	Working memory and verbal memory consolidation significantly associated with sleep efficiency
	Klingelhofer et al., 2016 [32]	Triaxial wrist-worn device	•60 participants with PD •6 days and nights	Parkinson's Disease Sleep Scale	Percentage of time spent immobile correlated moderately with sleep/fatigue questions of the NMSQ and with PDSS
Excessive daytime sleepiness	Kotschet et al., 2014 [33]	Triaxial wrist-worn device	•68 participants with PD •6 days and nights	Epworth Sleepiness Scale	Percentage of time spent immobile was significantly higher in those with ESS score ≥ 10
	Bolitho et al., 2013 [77]	Actigraphy (triaxial wrist-worn device)	•85 participants with PD •21 healthy controls •6 days and nights	Epworth Sleepiness Scale	Daytime inactivity measures did not correlate with ESS
Cognition	Bolitho et al., 2013 [77]	Actigraphy (triaxial wrist-worn device)	•85 participants with PD •21 healthy controls •6 days and nights	Cambridge Neuropsychological Test Automated Battery Mini Mental State Examination	Participants with excessive sleepiness had a trend towards poorer working memory
	Bloem et al., 2019 [47]	Triaxial sensor protocol	•650 participants with PD •2 years	MDS-UPDRS part I Montreal Cognitive Assessment Phonemic and semantic Fluency Brixton Spatial 15 Words Test Benton Judgment of Line Orientation Letter Number Sequencing Symbol Digit Modalities	Not available
	Weiss et al., 2019 [45]	Body fixed sensor	•96 participants with PD •One-off session	MMSE Montreal Cognitive Assessment MMSE	Timed up-and-go strategies were not related to cognitive function

(continued on next page)

Table 1 (continued)

Non motor symptom	Study	Remote monitoring device	Number of participants and duration of monitoring	Validation against	Measure used and findings
Impulse control disorder	van Uem et al., 2018 [44]	Home-based sensor	•47 participants with PD •3 days	MMSE	Significant associations between % sedentary and active episodes and MMSE, also with number of sedentary bouts
	Wu et al., 2018 [46]	Actigraphy (triaxial wrist-worn device)	•35 participants with PD •7–10 days		Less stable day-to-day rest-activity rhythm was associated with poorer executive, visuospatial, and psychomotor functioning, but not memory
	Evans et al., 2014 [39]	Triaxial wrist-worn device	•25 participants with PD •6 days and nights	Neuropsychiatric testing Questionnaire for Impulsive-Compulsive disorder (QUIP)	Number of medication acknowledgements correlated significantly with QUIP scores
	Sringean et al., 2016 [36]	Stationary homebased sensor	•19 participants with PD (and their partners) •1 night	Amount of times getting up at night for toilet visits	Sensor measured the amount of times that participants got out of bed; significant discrepancy between partner reported and objective measure
Gastrointestinal	Kyritsis et al., 2021 [78]	Triaxial wrist-worn device	•21 participants with PD •7 healthy controls	Time to move food from plate to mouth	Objective measure for time taken

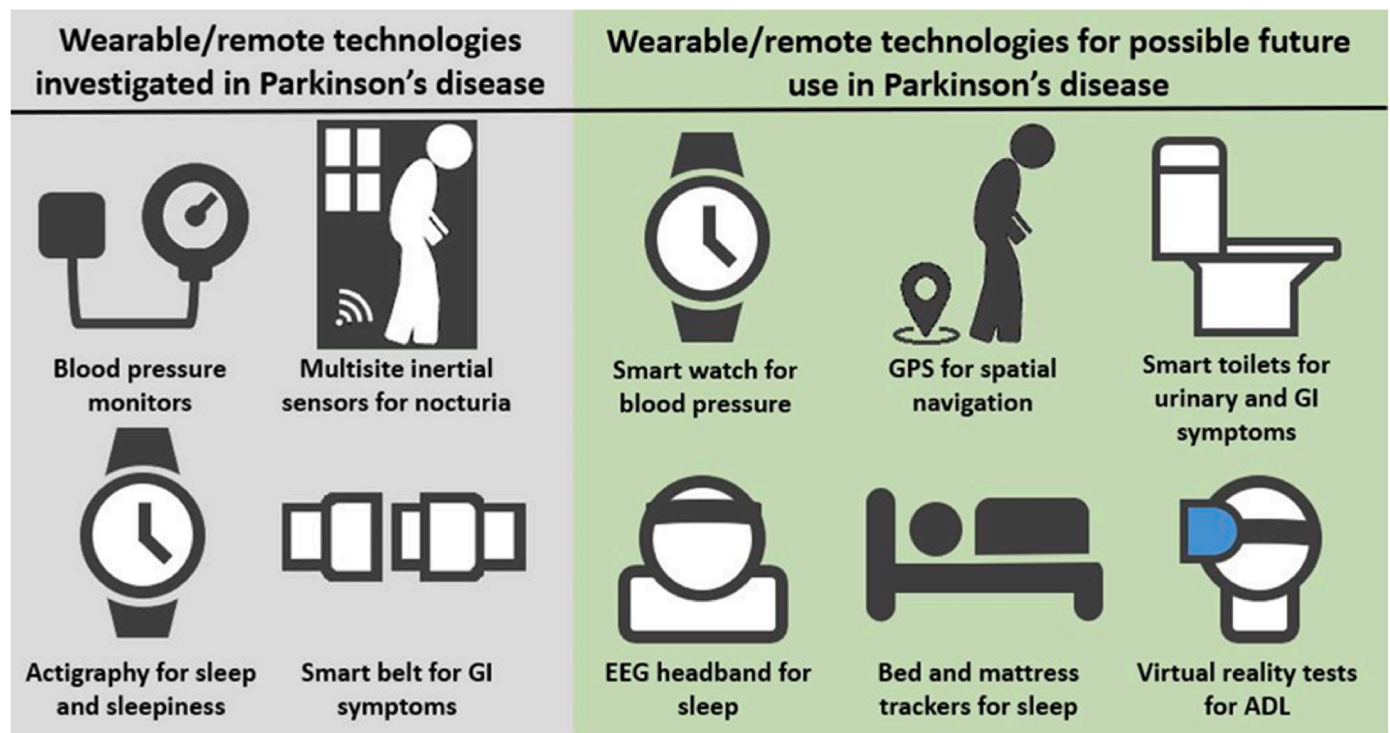


Figure 1. Examples of non-motor areas in Parkinson's disease where wearable and remote technologies have been investigated and non-motor areas where further developments are expected based on technologies available in other conditions. Abbreviations: GI: gastrointestinal; GPS: global positioning system; ADL: activities of daily living.

regarding prevalence (20% up to 80%) reported in PD cross-sectional subjective assessments [24]. The data related to its progression during the course of the disease are heterogeneous, but nonetheless sleep problems have a high impact on quality of life in PD and are often missed in outpatient settings [25–27].

Polysomnography (PSG) remains the gold standard for monitoring or diagnosing sleep dysfunction in PD, but is expensive, not widely available and requires patients to stay in bespoke facilities overnight. Wearable sensors would offer an alternative as a simpler, cheaper, and probably effective strategy. Nocturnal accelerometers are already in relatively wide-spread use for sleep monitoring and are used as an outcome measure in research settings. These do not include EEG recordings, which are required for direct assessment of sleep function, but only indirectly measure sleep-associated movements. Wrist worn

actigraphy, containing tri-axial accelerometers, quantifies the amount of motor activity during daytime and night-time, as a measure of sleep and physiological diurnal patterns, and was approved by FDA to measure limb activity associated with movement during sleep for physiologic applications [10]. Several studies have shown the usefulness of actigraphy in PD and this has been recently reviewed by Zampogna et al. [28]. Examples of the use of actigraphy include the findings by e.g. Perez-Lloret et al. reported that actigraphy data in PD significantly correlated with PD Sleep Scale (PDSS) and patient-completed diary data related to sleep quality and daytime somnolence [29]. Maglione and colleagues [10] reported a positive correlation of night-time actigraphy for the assessment of sleep quality and quantity in PD with PSG showing that actigraphy may be useful as a measurement for total sleep time, sleep efficiency, and wake time after sleep onset although with some

variability. However, as actigraphy records bouts of activity, there are difficulties in distinguishing Rapid Eye Movement Behaviour Disorder (RBD) from awake time using actigraphy. Several studies have reported the use of actigraphy to detect RBD [30,31], in which PD patients with RBD had significantly higher numbers of bouts of activity, scored as “awake”, on actigraphy. When compared to an RBD questionnaire, the actigraphy outcomes had low sensitivity for detecting RBD.

Tri-axial accelerometers are similar to actigraphy but are able to better quantify the amount of motor activity. Using such a device, Klingelhofer et al. reported that periods of immobility (periods during which no significant motor activity was detected) correlated well with PD Sleep Scale (PDSS) [32] although the association between wearables sensor output and motor activity captured by Hauser diary data was poor, perhaps supporting the benefits of objective rather than subjective (diary-based) outcomes. For daytime sleepiness, Kotschet et al. showed that the immobility measure of a tri-axial accelerometer was correlated with high Epworth Sleepiness Scores (ESS) [33].

Future developments in this field will be likely to draw from the experience gained in other fields of neurology, including Alzheimer disease. Examples of remote sleep measurement that are likely to make their way into PD are mobile phone sleep trackers, bed- or under-mattress fitted sensors (‘smart beds’), and wearable electroencephalogram headbands [34], but these have yet to be validated for use in PD. Especially ‘smart beds’ could prove useful and some evidence has already been presented that they are able to quantify nocturnal movements, including turning, being in upright position and walking during nocturnal period, in PD [35]. The usefulness of such sleep measurements is contained in its objectiveness, instead of patient and carer (sleep) diaries, which come with inherent inaccuracies and can be discrepant between patients and carer [36].

3.4. Impulse control disorder

Impulse control disorders (ICD) are characterised by the inability to assert self-control in emotions and behaviours, leading to compulsive and/or impulsive actions that harm oneself or others. The pathways involved in ICD have been implicated in rapid eye movement sleep behaviour disorder, constipation, and cognitive impairment [37]. Despite it being an important problem in PD [38], only one study has examined the role of wearables in ICD. Using a 3-axial accelerometer device, Evans and colleagues showed that ratings of ICD, in the form of Questionnaire for Impulsive-Compulsive Disorder in Parkinson’s Disease-Rating Scale (QUIP-RS) scores, was strongly positively associated with the number of acknowledgements per intake of oral medication in a small cohort of 25 PD patients. The intake was recorded by having the patient record the intake of medication by pressing a button on the watch; for this simple procedure it would not be necessary to have a tri-axial accelerometer or similar device but given the ease with which this can be recorded it would be easy to add it as a feature to any wearable device. This is also one of the few studies looking at wearable outcome measures that do not rely on motor markers to serve as a surrogate, but instead relied on assessing ICD severity by the amount of times a patient acknowledged the intake of medication using a paradigm embedded in the wearable device use [39].

Further developments in the objective capture of ICD could involve the analysis and quantification of internet use as it has been suggested these are linked in PD patients. More specifically, Wu et al. showed that PD patients with ICDs had a relative increased tendency towards excessive use of the Internet compared to those without ICDs as well as healthy controls [40]. However, in this study the information on internet use was gathered through means of a face-to-face structured interview and all participants had specifically consented to this, in addition to the self-reported documentation of type of websites they spend most time on whilst online. This is likely to be a limiting factor in the further development of objective measures for ICD based on Internet usage, as well as the clear privacy-related aspects.

3.5. Cognition

In recent years many forms of digital technology have been developed to measure cognitive performance. Although many of these technologies have not been tested in people with PD, there are a number of studies in Alzheimer’s disease. Due to its nature, digital health technologies assessing cognition range from wearable sensors to phone apps covering various aspects of cognitive function, such as the “Remote Assessment of Disease and Relapse – Alzheimer’s Disease” (RADAR-AD), using remote monitoring to actively and passively measure cognitive and affective biomarkers [34]. Examples of how cognitive performance can be measured include the passive use of Global Positioning System (GPS) movement trajectories or deviation from navigation tools for spatial navigation and memory, or the more active use of phone apps to measure performance on gamified/virtual reality tests as a measure for planning skills and task completion [34]. Other examples include, but are not limited to, app based technologies to assess spatial navigation, memory and other cognitive functions, phone app measurements using the performance on gamified/virtual reality tests for planning skills, smart home sensors for opening/closing of doors and window as a measure for daily activities, and speech analysis for dysnomia (<https://mezur.iohttps://altoida.com>) [34].

In PD, several studies have shown that gait parameters measured by conventional wearable triaxial sensors could be useful as an indirect indicator of cognitive decline, although further studies are required to assess confounders for the observed associations, and ideally such monitoring should move away from indirect markers of cognitive performance. A UK based study measured gait parameters using a single axis sensor and reported specific patterns for dementia typical for PD, dementia with Lewy bodies, and Alzheimer’s disease [41]. Terashi and colleagues have recently shown that in a cohort of 106 Japanese non fluctuating PD patients the gait acceleration amplitude showed a moderate positive association with Mini Mental State Examination (MMSE) scores [42]. This latter relation remained significant after the correction for UPDRS postural instability and gait disorder scores. The same group of researchers reported similar findings in drug-naïve PD patients, where daily physical activity was moderately positively associated with Frontal Assessment Battery and Behavioural Assessment of Dysexecutive Function scores. Significant associations were not present for other cognitive assessments, including MMSE, Beck Depression Inventory and Starkstein’s apathy scores [43]. In another study, in a cohort of 47 German PD patients, higher levels of daily activity measured with a back worn 3D accelerometer were associated with better cognitive scores [44]. However, Weiss and colleagues were unable to demonstrate a relation between timed up-and-go assessment, as measured by a body-fixed sensor, in PD patients with cognitive outcome measures (MoCA and MMSE) [45].

Recently, Mirelman and colleagues showed that nocturnal movements, including turning and being in upright position and walking during nocturnal period, were correlated to dysexecutive patterns using Trail Making Test scores which were inversely correlated to the number of rotations during the night. In addition, it was shown that Non-Motor Symptoms Scale scores were also inversely associated with turning in bed at night and nocturia [35]. In addition, circadian disruption, independent of sleep, has been investigated as a marker for cognition, and a decreased day-to-day rest-activity rhythm, as measured by actigraphy, was associated with poorer executive, visuospatial, and psychomotor functioning. Interdaily stability of circadian patterns predicted 14% of the variation occurring in executive function, psychomotor and visuospatial performance in a cohort of 35 PD patients [46].

A prospective, longitudinal, single-centre cohort study known as the ‘Personalized Parkinson Project’, is aiming to address the usefulness of a highly advanced smartwatch (including 3-axial accelerometers, a goniometer, a barometer, and sensors for skin temperature, environmental light and sound) in a large cohort who will wear the watch for up to 3 years. This study also includes a wide battery of neuro-psychological

assessments that will be measured annually as outcome in 650 participants. This study is currently underway, and the results are awaited [47].

3.6. Depressive symptoms

Even though no studies appear to exist looking at any direct relationship between depressive symptoms and measurable wearable sensor outcomes in PD, two studies have shown some evidence for associated changes that might be indicative of depressive symptoms. One study reported that PD patients with depressive symptoms showed a more pronounced systolic blood pressure drop on head up tilting and a higher prevalence of orthostatic hypotension compared to non-depressed patients even though there were no 24 h BP recordings performed in either group [48]. Similarly, PD patients with a geriatric depression score of five or over had higher adjusted levels of systolic, diastolic, and mean blood pressure dipping in addition to nocturnal high systolic pressure, and the presence of moderate to severe depressive symptoms was inversely associated with systolic dipping in a regression model [49]. Even though such measurements could be arguably used to capture depressive symptoms, it may be better to rely on more direct measures rather than surrogate markers as these often rely on associations and could be confounded by many factors, such as disease duration and age.

3.7. Gastrointestinal

Gastrointestinal dysfunction in PD affects the whole gastrointestinal tract and can be observed in each stage of the disease, from the prodromal to the advanced phases [50]. Especially constipation is a common feature with an overall prevalence ranging from 11 to 83%, and is considered as one of the earliest symptoms in PD and a risk factor for the development of this condition [51]. Also, other gastrointestinal problems, including dysphagia, are common in the later stages of PD with a major impact on quality of life and a pivotal role in prognosis (morbidity and mortality) in advanced PD [52,53].

There are no validated direct measures of function of gastrointestinal dysfunction in PD, although such efforts are underway to test digital health technology measuring these symptoms in PD. In fact, recently a smart belt for such symptoms has been developed and has received a CE mark, showing the device meets European standards on safety, health or environmental requirements (<https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b77ecf58&appId=PPGMS>). The smart belt is composed of five sensors (four acoustic and one for electrogastrogram) and an elastic band. The device records bowel sounds (using the acoustic sensors) and the electrical activity generated by the muscles' contractions triggered by stomach and intestines during digestion (electrogastrogram sensor). To date, no results have been published regarding the use of this belt and its outcomes in PD. Currently also other efforts are being made to measure other gastrointestinal and associated symptoms in PD, including impulsive eating disorders, appetite-related NMS, such as weight change, as well as dysphagia. Here, "plate-to-mouth" time, measured through a tri-axial wrist-worn sensor, has already been validated as an objective measure for eating behaviour in PD [54].

3.8. Urinary

Urinary symptoms are common in PD, as shown by studies where night-time urinary frequency (nycturia) was reported by 53% of female and 63% of male PwP, but also showing common urinary urgency and daytime frequency [55]. Interestingly, several groups have separately reported that the presence of urinary symptoms at diagnosis is a significant biomarker for more rapid functional decline [56–60]. Capturing urinary symptoms in PD may, therefore, aid in other areas of PD in addition to their impact on quality of life.

Only nocturia has been studied using multisite inertial sensors in the

home setting, providing remote monitoring. In this study patients had an inert registration device mounted in their home which picked up data from a body-fixed sensor collecting quantitative nocturnal movements of PD patients and comparing these outcomes to patients and spouse reported outcomes. Here it was shown that nocturia, measured by the number of times a patient got out of bed during the night, could be effectively picked up by the sensors, supported by sleep diaries [36].

Future monitoring of urinary (and gastrointestinal) NMS in PD could be achieved by further developing and validating the use of 'smart toilets'. Such toilets are capable of calculating urine flow rate and volume, classifying stool according to the Bristol stool form scale, and able to identify individual users through their fingerprint and the distinctive anoderm features [61]. Such devices could hold great potential in measurement and classification of urinary NMS in PD.

4. Discussion

Currently very few objective measures for the multifaceted NMS of PD exist. As such, it is not surprising to find that studies have tried to objectify and quantify these symptoms in the form of wearable sensors (Table 1). Nonetheless, few studies have looked at deploying wearable and remote technology for the measurement and monitoring of NMS in PD, but some technologies used to measure NMS in other conditions hold promise for future use in PD (Fig. 1).

As with any other symptom, the objective measurement and digital monitoring of NMS in PD requires a consensus to evaluate the quality and usefulness of digital devices, including but not limited to clinical utility, user experience, and governance for collection [62]. An additional difficulty, unlike the case with motor symptoms, is posed by the fact that NMS are often difficult to measure. Several suggestions have been made towards a standardised approach for digital healthcare technology and one of the most recent ones, by Goldsack and colleagues, includes a three-step approach: (1) verification (systematic evaluation by manufacturers), (2) analytical validation (valuation of processed data and testing on human subjects), and (3) clinical validation (evaluation of identification, measurement, and prediction of meaningful clinical, biological, physical, functional state, or experience in the specified context of use) [62]. From the available evidence on digital health technology for NMS, studies identified here would fall into category 3, but only with regards to the identification element of this category. In addition, it should be noted that some evidence presented here is based on indirect markers for specific NMS based on motor outcomes. Nonetheless, such markers (mostly bradykinesia and dopaminergic by default) of NMS based on wearable and objective motor measures, might be a good starting point to improve at least some NMS in PD. As an example, the number of acknowledgements per intake of oral medication appears to be strongly correlated to repetitive behaviour which is typically seen with ICD [39]. In addition, arguments have been made to suggest that it is not necessary to have exact measurements of a NMS in question, as long as the symptom of interest can be related to an outcome and lead to a management pathway with therapeutic intervention after identification [63,64]. Focusing on what correlates best to subjective patient disability, rather than subjective assessments as many in-clinic assessments may be biased due to e.g. attentional bias [3].

Once devices and digital technology have been developed and validated for NMS in PD, a further distinction needs to be made to define how this technology is to be used in clinical practice. Here, the example set by the National Institute for Health and Care Excellence (NICE) in the United Kingdom can serve as a guide towards classification of this kind of technology for the use in PD. The NICE guidelines propose a three-tiered system to classify digital health technologies, where evidence tiers are cumulative which means that a technology must meet all standards in both previous tier(s) and its own tier. In tier 1 the digital technology has no measurable patient outcomes but provides services to the health and social care system; in tier 2 the technology informs about a condition, provides simple monitoring, or allows two-communication

between patient and health care professional; and in tier 3 the technology additionally allows for preventative changes, self-management, treatment, active monitoring, impact calculator, or diagnosis of a condition [65]. The majority of the current studies that have looked at remote monitoring for NMS in PD would classify as tier 2 and further efforts are needed to move to tier 3 where NMS outcomes can be measured directly and trigger an intervention. At this stage, current limitations to the objective measurement of NMS, including recall bias affecting outcomes depending on the clinical scales or diaries used for addressing the NMS [2,66,67], will have been overcome.

Other factors that need to be overcome when it comes to objective digital monitoring of NMS is compliance, especially given the fact that PD results in motor and cognitive impairment which may be relevant for at least some remote and wearable technologies. So far, limited evidence has shown that compliance levels with wearable technology is relatively high for PD patients. Cohen et al. showed that compliance rates were reduced by 30% over a 6-month period [68], confirmed by another study where the 6-month compliance rate was 62–68% in two cohorts of 953 participants in total [69]. The main predictors for adherence appear to be caregivers' burden and patients' self-rated health status [70]. The study by Cohen et al. also showed an interesting observation in that daily smartwatch data streaming patterns peaked around mid-day and dropped sharply in the evening hours [68], perhaps indicative of a physiological circadian pattern [71].

Examples on the use of wearable sensor outcomes to guide treatment decisions are already available, albeit mostly involving motor outcomes. One such study showed that the use of a tri-axial wrist worn device for monitoring motor outcomes had an additional benefit on the increase in On-time after pharmacist-led medication review in 27 patients with PD [72]. At the same time the use of the wearable sensor in this study did not improve non-motor outcomes, although it should be noted that only a dichotomous outcome measure, the Non-Motor Symptoms Questionnaire, was used and treatment decisions were based on motor outcomes only [72]. One could imagine, however, that if wearable sensor outcomes, as outlined in this review, are used to identify NMS that would otherwise go unrecognised, this would have a great impact on treatment and quality of life. Examples include depressive symptoms and cognitive impairment, which are not only debilitating in themselves, but are moreover independent risk factors for non-adherence [73], and recognition of these symptoms could additionally lead to motor outcome improvements.

5. Conclusions

Following the increased availability and use of wearable technology in PD, the focus of these technologies is now also slowly shifting towards the broad NMS spectrum in this disease. Here, we have aimed to provide an overview of the current knowledge on this topic and show that, although the nature of NMS makes them difficult to objectively measure, further development and building on experience gained in other conditions may still lead to feasible capture of NMS. Although it is difficult, based on the currently available evidence, to make recommendations for the use of digital technology outcomes for NMS in clinical practice, evidence for these devices is clearly evolving and such advice may become available in the not too distant future.

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References

- [1] S.A. Lowe, G. Ólaighin, Monitoring human health behaviour in one's living environment: a technological review, *Med. Eng. Phys.* 36 (2) (2014) 147–168.
- [2] M.K. Erb, D.R. Karlin, B.K. Ho, K.C. Thomas, F. Parisi, G.P. Vergara-Diaz, J. F. Daneault, P.W. Wacnik, H. Zhang, T. Kangarloo, C. Demanuele, C.R. Brooks, C. N. Detheridge, N. Shaafi Kabiri, J.S. Bhangu, P. Bonato, mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's disease, *NPJ Digit Med* 3 (2020) 6.
- [3] V. Robles-García, Y. Corral-Bergantiños, N. Espinosa, M.A. Jácome, C. García-Sancho, J. Cudeiro, P. Arias, Spatiotemporal gait patterns during overt and covert evaluation in patients with Parkinson's disease and healthy subjects: is there a Hawthorne effect? *J Appl Biomech* 31(3) (2015) 189–194.
- [4] A. Channa, N. Popescu, V. Ciobanu, Wearable Solutions for Patients with Parkinson's Disease and Neurocognitive Disorder: A Systematic Review, *Sensors*, Basel, 2020, 20(9).
- [5] R. Pahwa, F. Bergquist, M. Horne, M.E. Minshall, Objective measurement in Parkinson's disease: a descriptive analysis of Parkinson's symptom scores from a large population of patients across the world using the Personal KinetiGraph®, *J Clin Mov Disord* 7 (2020) 5.
- [6] A. Zampogna, I. Mileti, E. Palermo, C. Celletti, M. Paoloni, A. Manoni, I. Mazzetta, G. Dalla Costa, C. Pérez-López, F. Camerota, L. Leocani, J. Cabestany, F. Irrera, A. Suppa, Fifteen Years of Wireless Sensors for Balance Assessment in Neurological Disorders, *Sensors*, Basel, 2020, 20(11).
- [7] A.L. Silva de Lima, T. Smits, S.K.L. Darweesh, G. Valenti, M. Milosevic, M. Pijl, H. Balduw, N.M. de Vries, M.J. Meinders, B.R. Bloem, Home-based monitoring of falls using wearable sensors in Parkinson's disease, *Movement Disorders* 35 (1) (2020) 109–115.
- [8] Z. Wu, X. Jiang, M. Zhong, B. Shen, J. Zhu, Y. Pan, J. Dong, P. Xu, W. Zhang, L. Zhang, Wearable sensors measure ankle joint changes of patients with Parkinson's disease before and after acute levodopa challenge, *Parkinson's Dis.* 2020 (2020) 2976535.
- [9] D.J. van Wamelen, P. Martinez-Martin, D. Weintraub, A. Schrag, A. Antonini, C. Falup-Pecurariu, P. Odin, K. Ray Chaudhuri, The Non-motor Symptoms Scale in Parkinson's Disease: Validation and Use, *Acta Neurologica Scandinavica*, 2020.
- [10] J.E. Maglione, L. Liu, A.B. Neikrug, T. Poon, L. Natarajan, J. Calderon, J. A. Avanzino, J. Corey-Bloom, B.W. Palmer, J.S. Lored, S. Ancoli-Israel, Actigraphy for the assessment of sleep measures in Parkinson's disease, *Sleep* 36 (8) (2013) 1209–1217.
- [11] M.D. Kruizinga, F.E. Stuurman, V. Exadaktylos, R.J. Doll, D.T. Stephenson, G. J. Groeneveld, G.J.A. Driessen, A.F. Cohen, Development of novel, value-based, digital endpoints for clinical trials: a structured approach toward fit-for-purpose validation, *Pharmacol. Rev.* 72 (4) (2020) 899–909.
- [12] R. Bhidayasiri, P. Martinez-Martin, Clinical Assessments in Parkinson's Disease: Scales and Monitoring, *International Review of Neurobiology*, Elsevier, 2017, pp. 129–182.
- [13] A. Antonini, A.J. Stoessl, L.S. Kleinman, A.M. Skalkick, T.S. Marshall, K.R. Sail, K. Onuk, P.L.A. Odin, Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach, *Curr. Med. Res. Opin.* 34 (12) (2018) 2063–2073.
- [14] R. Lakshminarayana, D. Wang, D. Burn, K.R. Chaudhuri, C. Galtrey, N.V. Guzman, B. Hellman, J. Ben, S. Pal, J. Stamford, M. Steiger, R.W. Stott, J. Teo, R.A. Barker, E. Wang, B.R. Bloem, M. van der Eijk, L. Rochester, A. Williams, Using a smartphone-based self-management platform to support medication adherence and clinical consultation in Parkinson's disease, *NPJ Parkinson's disease* 3 (2017) 2.
- [15] M. Bouhaddi, F. Vuillier, J.O. Fortrat, S. Cappellet, M.T. Henriet, L. Rumbach, J. Regnard, Impaired cardiovascular autonomic control in newly and long-term-treated patients with Parkinson's disease: involvement of L-dopa therapy, *Auton. Neurosci.* : basic & clinical 116 (1–2) (2004) 30–38.
- [16] R.B. Postuma, J.F. Gagnon, A. Pelletier, J. Montplaisir, Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies, *Mov. Disord.* 28 (5) (2013) 597–604.
- [17] W.A. den Hartog Jager, J. Bethlem, The distribution of Lewy bodies in the central and autonomic nervous systems in idiopathic paralysis agitans, *J. Neurol. Neurosurg. Psychiatr.* 23 (1960) 283–290.
- [18] B.L. Ten Harsmen, A. van Rumund, M.B. Aerts, M.I. Bergkamp, R.A.J. Esselink, E. Richard, F.J.A. Meijer, B.R. Bloem, D.J. van Wamelen, Clinical correlates of cerebral white matter abnormalities in patients with Parkinson's disease, *Park. Relat. Disord.* 49 (2018) 28–33.
- [19] R. Freeman, W. Wieling, F.B. Axelrod, D.G. Benditt, E. Benarroch, I. Biaggioni, W. P. Cheshire, T. Chelmsky, P. Cortelli, C.H. Gibbons, D.S. Goldstein, R. Hainsworth, M.J. Hiltz, G. Jacob, H. Kaufmann, J. Jordan, L.A. Lipsitz, B.D. Levine, P.A. Low, C. Mathias, S.R. Raj, D. Robertson, P. Sandroni, I. Schatz, R. Schondorff, J. M. Stewart, J.G. van Dijk, Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome, *Clin. Auton. Res.* : official journal of the Clinical Autonomic Research Society 21 (2) (2011) 69–72.
- [20] A.M. Hellman, S.P. Shah, S.M. Pawlowski, J.E. Duda, J.F. Morley, Continuous non-invasive monitoring to detect covert autonomic dysfunction in Parkinson's disease, *Park. Relat. Disord.* 21 (7) (2015) 723–728.
- [21] F. Vallelonga, A. Romagnolo, A. Merola, G. Sobrero, C. Di Stefano, V. Milazzo, J. Burrello, A. Burrello, M. Zibetti, A. Milan, F. Veglio, S. Maule, Detection of orthostatic hypotension with ambulatory blood pressure monitoring in Parkinson's disease, *Hypertens. Res.* 42 (10) (2019) 1552–1560.

- [22] C. Hahnen, C.G. Freeman, N. Haldar, J.N. Hamati, D.M. Bard, V. Murali, G.J. Merli, J.I. Joseph, N. van Helmond, Accuracy of vital signs measurements by a smartwatch and a portable health device: validation study, *JMIR Mhealth Uhealth* 8 (2) (2020) e16811.
- [23] N. van Helmond, C.G. Freeman, C. Hahnen, N. Haldar, J.N. Hamati, D.M. Bard, V. Murali, G.J. Merli, J.I. Joseph, The accuracy of blood pressure measurement by a smartwatch and a portable health device, *Hosp. Pract.* 47 (4) (1995) 211–215, 2019.
- [24] L.M. Chahine, A.W. Amara, A. Videnovic, A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015, *Sleep Med. Rev.* 35 (2017) 33–50.
- [25] M. Politis, K. Wu, S. Molloy, G.B. P. K.R. Chaudhuri, P. Piccini, Parkinson's disease symptoms: the patient's perspective, *Mov. Disord.* : official journal of the Movement Disorder Society 25 (11) (2010) 1646–1651.
- [26] K.R. Chaudhuri, C. Prieto-Jurcynska, Y. Naidu, T. Mitra, B. Frades-Payo, S. Tluk, A. Ruessmann, P. Odin, G. Macphree, F. Stocchi, W. Ondo, K. Sethi, A.H. Schapira, J.C. Martinez Castrillo, P. Martinez-Martin, The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire, *Mov. Disord.* : official journal of the Movement Disorder Society 25 (6) (2010) 704–709.
- [27] P. Gros, A. Videnovic, Overview of sleep and circadian rhythm disorders in Parkinson disease, *Clin. Geriatr. Med.* 36 (1) (2020) 119–130.
- [28] A. Zampogna, A. Manoni, F. Asci, C. Liguori, F. Irrera, A. Suppa, Shedding Light on Nocturnal Movements in Parkinson's Disease: Evidence from Wearable Technologies, *Sensors*, Basel, 2020, 20(18).
- [29] S. Perez-Lloret, M. Rossi, M.I. Nouzeilles, C. Trenkwalder, D.P. Cardinali, M. Merello, Parkinson's disease sleep scale, sleep logs, and actigraphy in the evaluation of sleep in parkinsonian patients, *J. Neurol.* 256 (9) (2009) 1480–1484.
- [30] S.L. Naismith, N.L. Rogers, J. Mackenzie, I.B. Hickie, S.J. Lewis, The relationship between actigraphically defined sleep disturbance and REM sleep behaviour disorder in Parkinson's Disease, *Clin. Neurol. Neurosurg.* 112 (5) (2010) 420–423.
- [31] M. Louter, J.B. Arends, B.R. Bloem, S. Overeem, Actigraphy as a diagnostic aid for REM sleep behavior disorder in Parkinson's disease, *BMC Neurol.* 14 (2014) 76.
- [32] L. Klingelhoefer, A. Rizo, A. Sauerbier, S. McGregor, P. Martinez-Martin, H. Reichmann, M. Horne, K.R. Chaudhuri, Night-time sleep in Parkinson's disease - the potential use of Parkinson's KinetiGraph: a prospective comparative study, *Eur. J. Neurol.* 23 (8) (2016) 1275–1288.
- [33] K. Kotschet, W. Johnson, S. McGregor, J. Kettlewell, A. Kyoong, D.M. O'Driscoll, A. R. Turton, R.I. Griffiths, M.K. Horne, Daytime sleep in Parkinson's disease measured by episodes of immobility, *Park. Relat. Disord.* 20 (6) (2014) 578–583.
- [34] A.P. Owens, C. Hinds, N.V. Manyakov, T.G. Stavropoulos, G. Lavelle, D. Gove, A. Diaz-Ponce, D. Aarsland, Selecting remote measurement technologies to optimize assessment of function in early alzheimer's disease: a case study, *Front. Psychiatr.* 11 (2020) 582207.
- [35] A. Mirelman, I. Hillel, L. Rochester, S. Del Din, B.R. Bloem, L. Avanzino, A. Nieuwboer, I. Maidan, T. Herman, A. Thaler, T. Gurevich, M. Kestenbaum, A. Orr-Urtreger, M. Brys, J.M. Cedarbaum, N. Giladi, J.M. Hausdorff, Tossing and turning in bed: nocturnal movements in Parkinson's disease, *Mov. Disord.* : official journal of the Movement Disorder Society 35 (6) (2020) 959–968.
- [36] J. Sringean, P. Taechalerpaisarn, C. Thanawattano, R. Bhidayasiri, How well do Parkinson's disease patients turn in bed? Quantitative analysis of nocturnal hypokinesia using multisite wearable inertial sensors, *Park. Relat. Disord.* 23 (2016) 10–16.
- [37] A. Augustine, C.A. Winstanley, V. Krishnan, Impulse control disorders in Parkinson's disease: from bench to bedside, *Front. Neurosci.* 15 (2021) 654238.
- [38] I. Rieu, J.L. Houeto, B. Pereira, I. De Chazeron, A. Bichon, I. Chereau, M. Ulla, C. Brefel-Courbon, F. Ory-Magne, K. Dujardin, F. Tison, P. Krack, F. Durif, Impact of mood and behavioral disorders on quality of life in Parkinson's disease, *J. Parkinsons Dis.* 6 (1) (2016) 267–277.
- [39] A.H. Evans, J. Kettlewell, S. McGregor, K. Kotschet, R.I. Griffiths, M. Horne, A conditioned response as a measure of impulsive-compulsive behaviours in Parkinson's disease, *PLoS One* 9 (2) (2014) e89319.
- [40] K. Wu, M. Politis, S.S. O'Sullivan, A.D. Lawrence, S. Warsi, A. Lees, P. Piccini, Problematic Internet use in Parkinson's disease, *Park. Relat. Disord.* 20 (5) (2014) 482–487.
- [41] R. Mc Ardle, S. Del Din, B. Galna, A. Thomas, L. Rochester, Differentiating dementia disease subtypes with gait analysis: feasibility of wearable sensors? *Gait Posture* 76 (2020) 372–376.
- [42] H. Terashi, T. Taguchi, Y. Ueta, Y. Okubo, H. Mitoma, H. Aizawa, Analysis of non-invasive gait recording under free-living conditions in patients with Parkinson's disease: relationship with global cognitive function and motor abnormalities, *BMC Neurol.* 20 (1) (2020) 161.
- [43] H. Terashi, T. Taguchi, Y. Ueta, H. Mitoma, H. Aizawa, Association of daily physical activity with cognition and mood disorders in treatment-naïve patients with early-stage Parkinson's disease, *J. Neural. Transm.* 126 (12) (2019) 1617–1624.
- [44] J.M.T. van Uem, B. Cerff, M. Kampmeyer, J. Prinzen, M. Zuidema, M.A. Hobert, S. Gräber, D. Berg, W. Maetzler, I. Liepelt-Scarfone, The association between objectively measured physical activity, depression, cognition, and health-related quality of life in Parkinson's disease, *Park. Relat. Disord.* 48 (2018) 74–81.
- [45] A. Weiss, T. Herman, A. Mirelman, S.S. Shatzky, N. Giladi, L.L. Barnes, D. A. Bennett, A.S. Buchman, J.M. Hausdorff, The transition between turning and sitting in patients with Parkinson's disease: a wearable device detects an unexpected sequence of events, *Gait Posture* 67 (2019) 224–229.
- [46] J.Q. Wu, P. Li, K. Stavitsky Gilbert, K. Hu, A. Cronin-Golomb, Circadian rest-activity rhythms predict cognitive function in early Parkinson's disease independently of sleep, *movement disorders clinical practice* 5(6), 2018, pp. 614–619.
- [47] B.R. Bloem, W.J. Marks Jr., A.L. Silva de Lima, M.L. Kuijff, T. van Laar, B.P. F. Jacobs, M.M. Verbeek, R.C. Helmich, B.P. van de Warrenburg, L.J.W. Evers, J. Int'Hout, T. van de Zande, T.M. Snyder, R. Kapur, M.J. Meinders, The Personalized Parkinson Project: examining disease progression through broad biomarkers in early Parkinson's disease, *BMC Neurol.* 19 (1) (2019) 160.
- [48] H.E. Park, J.S. Kim, Y.S. Oh, I.S. Park, J.W. Park, I.U. Song, K.S. Lee, Autonomic nervous system dysfunction in patients with Parkinson disease having depression, *J. Geriatr. Psychiatr. Neurol.* 29 (1) (2016) 11–17.
- [49] D.L. Vetrano, M.S. Pisciotto, M.R. Lo Monaco, G. Onder, A. Laudisio, V. Brandi, D. La Carpi, M. Guglielmo, A. Nacchia, D. Fusco, D. Ricciardi, A.R. Bentivoglio, R. Bernabei, G. Zuccala, Association of depressive symptoms with circadian blood pressure alterations in Parkinson's disease, *J. Neurol.* 262 (11) (2015) 2564–2571.
- [50] R.F. Pfeiffer, Gastrointestinal dysfunction in Parkinson's disease, *Curr. Treat. Options Neurol.* 20 (12) (2018) 54.
- [51] K.L. Adams-Carr, J.P. Bestwick, S. Shribman, A. Lees, A. Schrag, A.J. Noyce, Constipation preceding Parkinson's disease: a systematic review and meta-analysis, *J. Neurol. Neurosurg. Psychiatry* 87 (7) (2016) 710–716.
- [52] R. Cilia, E. Cereda, C. Klersy, M. Canesi, A.L. Zecchinelli, C.B. Mariani, S. Tesi, G. Sacilotto, N. Meucci, M. Zini, C. Ruffmann, I.U. Isaia, S. Goldwurm, G. Pezzoli, Parkinson's disease beyond 20 years, *J. Neurol. Neurosurg. Psychiatr.* 86 (8) (2015) 849–855.
- [53] M. Fabbri, M. Coelho, D. Abreu, L.C. Guedes, M.M. Rosa, C. Godinho, R. Cardoso, I. Guimaraes, A. Antonini, M. Zibetti, L. Lopiano, J.J. Ferreira, Dysphagia predicts poor outcome in late-stage Parkinson's disease, *Park. Relat. Disord.* 64 (2019) 73–81.
- [54] K. Kyritsis, P. Fagerberg, I. Ioakimidis, L. Klingelhoefer, H. Reichmann, A. Delopoulos, Using imu sensors to assess motor degradation of pd patients by modeling in-meal plate-to-mouth movement elongation, in: 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), IEEE, 2020, pp. 494–497.
- [55] R. Sakakibara, H. Shinotoh, T. Uchiyama, M. Sakuma, M. Kashiwado, M. Yoshiyama, T. Hattori, Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease, *Auton. Neurosci.* 92 (1–2) (2001) 76–85.
- [56] P. Barone, A. Antonini, C. Colosimo, R. Marconi, L. Morgante, T.P. Avarello, E. Bottacchi, A. Cannas, G. Ceravolo, R. Ceravolo, G. Cicarelli, R.M. Gaglio, R. M. Giglia, F. Iemolo, M. Manfredi, G. Meco, A. Nicoletti, M. Pederzoli, A. Petrone, A. Pisani, F.E. Pontieri, R. Quatrone, S. Ramat, R. Scala, G. Volpe, S. Zappulla, A. R. Bentivoglio, F. Stocchi, G. Trianni, P.D. Dotto, The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease, *Mov. Disord.* : official journal of the Movement Disorder Society 24 (11) (2009) 1641–1649.
- [57] E. De Pablo-Fernandez, C. Tur, T. Revesz, A.J. Lees, J.L. Holton, T.T. Warner, Association of autonomic dysfunction with disease progression and survival in Parkinson disease, *JAMA neurology* 74 (8) (2017) 970–976.
- [58] M. Picillo, R. Palladino, P. Barone, R. Erro, C. Colosimo, R. Marconi, L. Morgante, A. Antonini, The PRIAMO study: urinary dysfunction as a marker of disease progression in early Parkinson's disease, *Eur. J. Neurol.* 24 (6) (2017) 788–795.
- [59] A. Ayala, J.M. Trivino-Juarez, M.J. Forjaz, C. Rodriguez-Blazquez, J.M. Rojo-Abuin, P. Martinez-Martin, Parkinson's disease severity at 3 years can be predicted from non-motor symptoms at baseline, *Front. Neurol.* 8 (2017) 551.
- [60] R. Erro, M. Picillo, M. Amboni, M. Moccia, C. Vitale, K. Longo, M.T. Pellecchia, G. Santangelo, P. Martinez-Martin, K.R. Chaudhuri, P. Barone, Nonmotor predictors for levodopa requirement in de novo patients with Parkinson's disease, *Mov. Disord.* : official journal of the Movement Disorder Society 30 (3) (2015) 373–378.
- [61] S.-m Park, D.D. Won, B.J. Lee, D. Escobedo, A. Esteve, A. Aalipour, T.J. Ge, J. H. Kim, S. Suh, E.H. Choi, A mountable toilet system for personalized health monitoring via the analysis of excreta, *Nature biomedical engineering* 4 (6) (2020) 624–635.
- [62] J.C. Goldsack, A. Coravos, J.P. Bakker, B. Bent, A.V. Dowling, C. Fitzer-Attas, A. Godfrey, J.G. Godino, N. Gujar, E. Izmailova, C. Manta, B. Peterson, B. Vandendriessche, W.A. Wood, K.W. Wang, J. Dunn, Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs), *NPJ Digit Med* 3 (2020) 55.
- [63] P. Odin, K.R. Chaudhuri, J. Volkman, A. Antonini, A. Storch, E. Dietrichs, Z. Pirtosek, T. Henriksen, M. Horne, D. Devos, F. Bergquist, Viewpoint and practical recommendations from a movement disorder specialist panel on objective measurement in the clinical management of Parkinson's disease, *NPJ Parkinson's disease* 4 (2018) 14.
- [64] W. Maetzler, J. Klucken, M. Horne, A clinical view on the development of technology-based tools in managing Parkinson's disease, *Mov. Disord.* 31 (9) (2016) 1263–1271.
- [65] National Institute for Health and Care Excellence, Evidence standards framework for digital health technologies (Corporate document ECD7), ., 2019.
- [66] M. Stacy, A. Bowron, M. Guttman, R. Hauser, K. Hughes, J.P. Larsen, P. LeWitt, W. Oertel, N. Quinn, K. Sethi, F. Stocchi, Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment, *Mov. Disord.* 20 (6) (2005) 726–733.
- [67] C. Ossig, F. Gandor, M. Fauser, C. Bosredon, L. Churilov, H. Reichmann, M. K. Horne, G. Ebersbach, A. Storch, Correlation of quantitative motor state assessment using a kinetograph and patient diaries in advanced PD: data from an observational study, *PLoS One* 11 (8) (2016) e0161559.

- [68] S. Cohen, Z. Waks, J.J. Elm, M.F. Gordon, I.D. Grachev, L. Navon-Perry, S. Fine, I. Grossman, S. Papapetropoulos, J.M. Savola, Characterizing patient compliance over six months in remote digital trials of Parkinson's and Huntington disease, *BMC Med. Inf. Decis. Making* 18 (1) (2018) 138.
- [69] A.L. Silva de Lima, T. Hahn, L.J.W. Evers, N.M. de Vries, E. Cohen, M. Afek, L. Bataille, M. Daeschler, K. Claes, B. Borojerd, D. Terricabras, M.A. Little, H. Baldus, B.R. Bloem, M.J. Faber, Feasibility of large-scale deployment of multiple wearable sensors in Parkinson's disease, *PLoS One* 12 (12) (2017) e0189161.
- [70] D. Gatsios, A. Antonini, G. Gentile, A. Marcante, C. Pellicano, L. Macchiusi, F. Assogna, G. Spalletta, H. Gage, M. Touray, L. Timotijevic, C. Hodgkins, M. Chondrogiorgi, G. Rigas, D.I. Fotiadis, S. Konitsiotis, Feasibility and utility of mHealth for the remote monitoring of Parkinson disease: ancillary study of the PD_manager randomized controlled trial, *JMIR Mhealth Uhealth* 8 (6) (2020) e16414.
- [71] D.J. van Wamelen, D. Urso, K.R. Chaudhuri, How Time Rules: diurnal Motor Patterns in de novo Parkinson's Disease, *J. Parkinsons Dis.* 11 (2) (2021) 695–702.
- [72] C. Stuijt, F. Karapinar-Çarkit, B. van den Bemt, T. van Laar, Effect of pharmacist-led interventions on (Non)Motor symptoms, medication-related problems, and quality of life in Parkinson disease patients: a pilot study, *Clin. Neuropharmacol.* 41 (1) (2018) 14–19.
- [73] J.E. Fleisher, M.B. Stern, Medication nonadherence in Parkinson's disease, *Curr. Neurol. Neurosci. Rep.* 13 (10) (2013) 382.
- [74] A. Nass, R.D. Nass, Actigraphic evidence for night-time hyperkinesia in Parkinson's disease, *Int. J. Neurosci.* 118 (2) (2008) 291–310.
- [75] K. Stavitsky, J.L. Saurman, P. McNamara, A. Cronin-Golomb, Sleep in Parkinson's disease: a comparison of actigraphy and subjective measures, *Park. Relat. Disord.* 16 (4) (2010) 280–283.
- [76] D.G. Gunn, S.L. Naismith, S.J. Bolitho, S.J. Lewis, Actigraphically-defined sleep disturbance in Parkinson's disease is associated with differential aspects of cognitive functioning, *J. Clin. Neurosci.* 21 (7) (2014) 1112–1115.
- [77] S.J. Bolitho, S.L. Naismith, P. Salahuddin, Z. Terpening, R.R. Grunstein, S.J. Lewis, Objective measurement of daytime napping, cognitive dysfunction and subjective sleepiness in Parkinson's disease, *PLoS One* 8 (11) (2013) e81233.
- [78] K. Kyritsis, P. Fagerberg, I. Ioakimidis, K.R. Chaudhuri, H. Reichmann, L. Klingelhöfer, A. Delopoulos, Assessment of real life eating difficulties in Parkinson's disease patients by measuring plate to mouth movement elongation with inertial sensors, *Sci. Rep.* 11 (1) (2021) 1632.